

REMARKS

Upon entry of the above amendment, claims 11- 14 and 20-30 will be pending in the present application. Applicants have canceled claims 15-19 without prejudice and reserve that right to pursue the subject matter in a subsequent Divisional application.

The specification provides support for the amendment to claims 11 and 12 and new claims 21-30 on page 1, lines 8-32 and Example 5 on pages 21-23. Claims 11, 21 and 26 are independent.

Applicants, for purpose of preliminary examination, elected  $\gamma$ -cyclodextrin as the chelator, although the full scope of the elected claims are understood to be examined after determining the patentability of the  $\gamma$ -cyclodextrin embodiment. Applicants confirm the elect of  $\gamma$ -cyclodextrin as the elected species for preliminary examination.

Applicants would like to thank the Examiner for the Interview of March 4, 2005. Applicants' representative found the interview both informative and effective. Applicants have attempted to reflect the intent from the interview with the above amendment and following remarks.

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USSN: 10/049,393

Issue Under 35 U.S.C. §112, first paragraph

Claims 11-13 and 20 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable all neuromuscular blocking drugs with all cyclodextrins. The Examiner asserts that the claims scope is not commensurate is scope with the specification.

During the Interview, the Examiner cited the DÉSIRÉ et al publication for disclosing that the neuromuscular blocking effect of sarin and soman may be reversed by the use of  $\beta$ -cyclodextrin.

The Examiner argues that DESIRE et al also disclosed that tabun is not reversed even though it is of a similar structure to sarin, concluding that the art is not predictable. Applicants respectfully traverse this assertion.

A clinically used neuromuscular blocking agent is an agent (two categories can be distinguished: depolarizing or a non-depolarizing, as explained on page 1 of the description) which acts by reversible binding to the (muscle) acetylcholine receptor and as such block the binding of the endogenous modulator acetylcholine. In practice muscle relaxation in a patient ensues on occupation of over ca 70% of the muscle acetylcholine receptors with a blocker. On application of a chemical chelator according to the present invention, part of the unbound blocker in the circulation is bound to the chemical chelator, thereby shifting the equilibrium of binding of blocker to the

acetylcholine receptor. As a result the percentage occupation of the acetylcholine receptors is quickly reduced to below 70%; upon which acetylcholine can again interact with the receptor so that the muscle tone returns.

In contrast, the nerve agents irreversibly inhibit the enzyme acetylcholine esterase (by covalently binding to the enzyme), the enzyme responsible for the hydrolysis of the neurotransmitter acetylcholine. On inactivation of the enzyme the concentration of acetylcholine rapidly rises and desensitizes the acetylcholine receptor. This process ultimately leads to neuromuscular block.

Therefore, one skilled in the art can conclude that the nerve agents do not bind to the muscle acetylcholine receptor at all. The detoxification process described by DESIRE relates to their observation that beta-cyclodextrin was found to be able to covalently react (phosphorylation of the cyclodextrin) with sarin and soman, and not with tabun and VX.

Consequently, one cannot impose the unpredictability disclosed in DESIRE et al on the present invention because DESTRE et al fails to disclose clinically-used neuromuscular blocking agents that act by reversible binding to acetylcholine receptor and the agents it does disclose act in a completely different manner.

Applicants assert that Examples 5 and 6 disclose a

representative amount of neuromuscular blocking agents that work within the scope of the present claims. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991).

Applicants respectfully request withdrawal of the 35 U.S.C. §112, first paragraph.

Issues Under 35 U.S.C. §103

Claims 11 and 13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over DESIRE et al (Experimentia, 1987). Applicants respectfully submit that patentable differences exist between the cited prior art and the present invention.

*Distinctions Between the Present Invention and DESIRE*

DÉSIRÉ et al discloses that sarin and soman are inactivated by cyclodextrins in vitro. The Examiner has acknowledged that the reference fails to specifically exemplify actual administration of a cyclodextrin to a subject, but merely suggests such administration. During the Interview of March 4, 2005, Applicants presented the present claims with the assertion

that DÉSIRÉ et al fails to disclose a clinically-used neuromuscular blocking agent which act by reversible binding to acetylcholine receptor.

As discussed above, sarin and soman are chemical warfare agents that react irreversibly to cause an increase in acetylcholine in a subject.

The Examiner agreed that NMBA used for clinical use are different than the neurotoxins described in DÉSIRÉ et al. DÉSIRÉ et al. fails to suggest the use of a clinically-used or surgical anesthesia NMBA. The Examiner must present a *prima facie* case of obviousness consisting of motivation or suggestion to modify or combine references such that one of ordinary skill in the art has a reasonable expectation of success of making the present composition. "Obviousness can only be established by combining or modifying the teaching of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP 2143.01, citing In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection.

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Allowable Subject Matter

Applicants appreciate the Examiner indicating that claims 12, 14, and 20 would be free of prior art and allowable if written to the recited NMBA and  $\gamma$ -CD. Applicants have amended the claim and have presented arguments that the present claims are now in condition for allowance.

Conclusion

Applicants has addressed every issued raised by the Examiner and respectfully submit that the present application is in condition for allowance.

If the Examiner believes for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

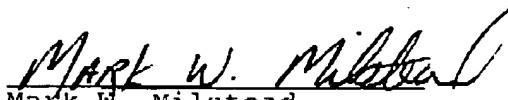
If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional

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fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17;  
particularly extension of time fees.

Respectfully submitted,

  
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